Respiratory Medicine (2014) 108, 405–412

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Home spirometry as early detector of azithromycin refractory bronchiolitis obliterans syndrome in lung transplant recipients

Claudia de Wall [a,*], Dettmer Sabine [b], Warnecke Gregor [c], Greer Mark [a], Haverich Axel [c], Fuehner Thomas [a], Welte Tobias [a], Gottlieb Jens [a]

[a] Department of Pulmonary Medicine, Hannover Medical School, Hannover, Germany
[b] Department of Radiology, Hannover Medical School, Hannover, Germany
[c] Department of Cardiothoracic, Transplantation and Vascular Surgery, Hannover Medical School, Hannover, Germany

Received 8 September 2013; accepted 30 December 2013
Available online 8 January 2014

KEYWORDS
Azithromycin;
Bronchiolitis;
Lung

Summary
Background: To evaluate the utility of home spirometry (HS) versus office spirometry (OS) in assessing treatment response to azithromycin in bronchiolitis obliterans syndrome (BOS).
Methods: 239 Lung transplant recipients were retrospectively studied. $\Delta FEV_1 \pm 10\%$ from FEV_1 at azithromycin initiation for $\geq$7 consecutive days in HS or $\geq$2 measures in OS were taken as cut-off for response or progression.
Results: Based upon HS, 161/239 (67%) patients were progressive despite macrolide, 19 of who exhibited transient improvement in FEV_1 (11%). Time to progression was 29 (13–96) days earlier with HS than in OS. Forty-six (19%) recipients responded in HS after median 81 (22–343) days, whilst 22% remained stable. Concordance in azithromycin treatment response between OS and HS was observed in 210 of 239 patients (88%). Response or stabilization conferred significant improvement in survival ($p = 0.005$). Transient azithromycin responders demonstrated improved survival when compared to azithromycin refractory patients ($p = 0.034$).
Conclusions: HS identified azithromycin refractory patients significantly earlier than OS, possibly facilitating aggressive treatment escalation that may improve long-term outcome.

Abbreviations: BAL, bronchoalveolar lavage; BOS, bronchiolitis obliterans syndrome; FEV_1, forced expiratory volume in one 1 s; HS, home spirometry; IQR, interquartile ranges; LTx, lung transplantation; OS, office spirometry; RAS, restrictive allograft syndrome.

* Corresponding author. Hannover Medical School, Department of Respiratory Medicine, Carl-Neuberg-Strasse 1, 30625 Hannover, Germany. Tel.: +49 511 532 3560; fax: +49 511 5328094.
E-mail addresses: dewall.claudia@freenet.de, dewall.claudia@mh-hannover.de, claudia.andre@arcor.de (C. de Wall).

http://dx.doi.org/10.1016/j.rmed.2013.12.016

Treatment response to azithromycin should be assessed 4 weeks after initiation. Responders demonstrated best survival, with even transient response conferring benefit. Macrolide-refractory BOS carried the worst prognosis.

Introduction

Lung transplantation (LTx) has become an accepted therapeutic option for selected patients with end-stage lung disease. Post-transplant survival continues to improve, but mean 5-year survival remains disappointingly low at 53% [1]. Bronchiolitis obliterans syndrome (BOS) remains the leading cause of death beyond the first year after transplantation [1], affecting almost half of all patients within 5 years. BOS is characterized by its unpredictable and variable clinical course, ranging from an insidious onset with gradual loss of pulmonary function over months to years, to an abrupt and severe decline in pulmonary function within a matter of weeks [2—4]. Whilst obliterative bronchiolitis is the presumed histopathological correlate, it is not consistently detectable by transbronchial biopsy and spirometry is routinely used as the agreed surrogate marker to diagnose and stage BOS [5]. Current treatment strategies for BOS include aggressive management of known risk factors as well as early identification of BOS and initiation of proposed treatments or re-transplantation.

Long-term azithromycin has been shown to improve FEV_1 and survival in up to 40% of BOS patients in various single-center studies [6—10]. Current data however, does not provide insight beyond initial response, with little being known about whether initial responders relapse later or whether non-responders stabilize after azithromycin initiation. Early azithromycin initiation prior to development of BOS stage 2 has been associated with a significant reduction in risk of death [9], suggesting the possibility of critical therapeutic windows for efficacy of some treatment options.

Given these issues, prompt assessment for therapeutic response with a view to treatment escalation in progressive patients is vital. Previous studies involving lung transplant recipients have demonstrated the benefits of daily home spirometry (HS) in detecting early changes in graft function [11—16]. In the current study, home spirometry data was used to evaluate treatment response after commencing azithromycin in LTx patients with BOS to evaluate if macrolide-refractory progression could be identified earlier than the present system of office spirometry (OS).

Materials and methods

A single-center retrospective analysis of all adult lung transplant recipients between 2003 and 2011 commenced on long-term azithromycin for bronchiolitis obliterans was performed.

Only patients with adequate adherence to home spirometry ($\geq$50% prescribed measures) and at least one follow-up visit after azithromycin initiation were included. Recipients with severe airway complications, unknown start or interrupted azithromycin treatment were excluded (Fig. 1). All patients were followed-up from azithromycin initiation until death, re-transplantation or to completion of the study on May 31, 2011.

Home spirometry (HS)

Patients were instructed on using a home spirometry device and asked to perform daily testing, ensuring that attempts were made at the same time each day. All patients used a handheld electronic spirometry system (VIASYS® Healthcare, Hoechberg, Germany) that collected and stored relevant expiratory flow—volume parameters including FEV_1. Following each attempt, a digital display on the spirometer indicated the current FEV_1 value along with a direct comparison to the patient's pre-programmed best FEV_1. Based on a "traffic light" system, the device displays green when $\geq$90% best FEV_1 is achieved, yellow for $<$90% but $\geq$80% and red for $<$80% best FEV_1. The device stores up to 450 measurements, which were routinely downloaded at each outpatient attendance and stored centrally in an electronic database. Patients were instructed to contact the transplant center within 24 h following a change in "colour" on the spirometer, regardless of symptoms.

Routine follow-up

Patients were followed-up at our specialized outpatient clinic with scheduled visits at 2- to 4- month intervals. Standard immunosuppression consisted of a triple-drug regimen including a calcineurin-inhibitor, prednisolone and either a cell-cycle-inhibitor or mTOR (mammalian target of rapamycin) inhibitor. After excluding alternate causes, azithromycin (as the standard neo-macrolide therapy) was commenced in all patients demonstrating a persistent deterioration in lung function below 80% baseline, with most patients receiving an initial loading dose of 500 mg daily for 3 days before continuing with 250 mg three times per week thereafter. Routine follow-up attendances included clinical examination, spirometry, capillary blood gas analysis and a chest x-ray. Bronchoscopy was routinely performed, based on interpretation of these findings to investigate suspected rejection, infection or airway complication.

BOS staging complied with the International Society of Heart and Lung Transplantation classification of bronchiolitis obliterans syndrome (BOS) [17]. Baseline FEV_1 was defined as the average of the two highest measurements obtained at least 3 weeks apart during postoperative course.

Restrictive allograft syndrome (RAS) was defined according to Sato et al. [18]. If TLC data were not available, RAS was defined by imaging (presence of parenchymal

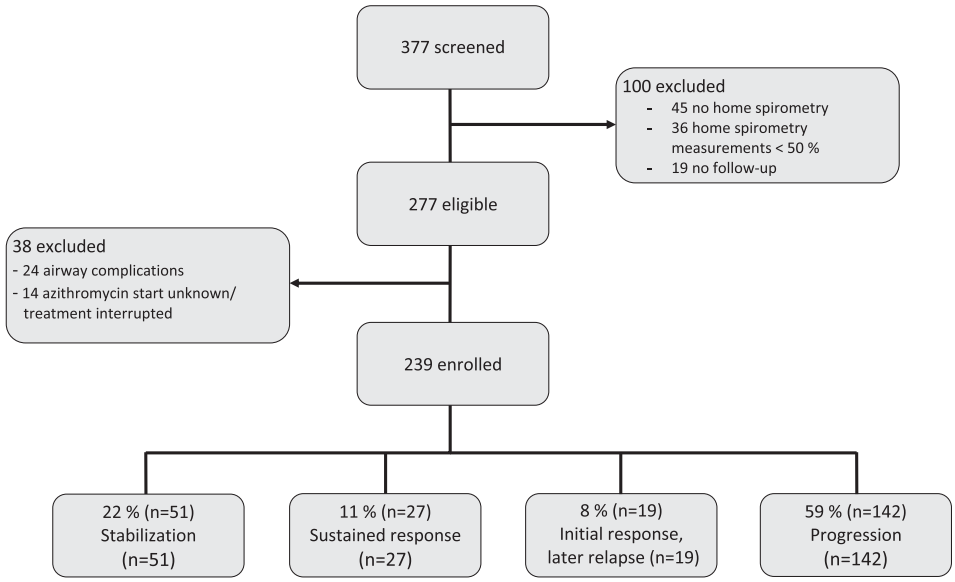

Figure 1 Enrollement of Patients with azithromycin treatment for bronchiolitis obliterans syndrome (2003—2011). Treatment response based upon HS.

infiltrates) and the absence of an obstructive pattern in pulmonary function test (FEV/FVC $>$ 0.7).

Interpretation of macrolide response

In *home spirometry (HS)*, patients demonstrating a $\geq$10% FEV_1 increase (compared to FEV_1 at start of azithromycin) from the baseline value over a period of 7 consecutive days were termed responders. Patients with a $\geq$10% FEV_1 loss over 7 consecutive days were classified as progressive. All remaining patients with FEV_1 values between 91 and 109% were considered stabilized. Patients who initially fulfilled the responder criteria, but subsequently progressed to $\leq$90% FEV_1 during follow-up, were termed transient responders.

With regard to *office spirometry (OS)*, the same cut-off values in %FEV_1 were used and considered relevant when arising in at least two consecutive OS measurements after excluding alternative causes. OS was performed in accordance to the published guidelines of the American Thoracic Society and European Respiratory Society [19].

The date of progression or response in HS and OS was defined as the first occasion on which the cut-off values were reached.

Statistical analysis

Data are reported as medians with interquartile ranges (IQR) and all reported p values are two-sided unless otherwise stated. For all analyses, p-values $<$0.05 were considered statistically significant. Category variables were analysed using either a chi-squared test or Fisher's exact test. Medians were compared using the Mann—Whitney test and the nonparametric Kruskal—Wallis-H test. Cohen's kappa coefficient was used as a measure of agreement for categorical items. Survival curves were constructed using Kaplan Meier method and compared using the log-rank test.

Results

Two hundred thirty-nine lung transplant recipients fulfilled inclusion criteria. Baseline characteristics of patients are listed in Table 1. Median follow-up was 22 (11—37) months. Median FEV_1 at azithromycin initiation was 67% (54—77) baseline, 21% had a restrictive phenotype. Sixty-seven percent of patients (161/239) demonstrated progression in HS. Nineteen patients (19/239, 8%) had an initial response but progressed during follow-up after 501 (232—1334) days and were considered transient responders. No transient responder stabilized. Time to progression was 61 (24—149) days according to HS and 90 (37—245) days according to OS. HS detected progression on average 29 (13—96) days earlier than outpatient measures. Median loss of FEV_1 in all progressive patients was 0.4 L (−17%) at the first visit defining progress in OS.

Nineteen percent of patients (46/239) responded to azithromycin after 81 (22—343) days on HS, compared to 222 (64—551) days on OS. HS detected treatment response on average 141 (42—208) days earlier than office measures. Twenty-two percent of patients (51/239) exhibited stabilized lung function after commencing macrolides. Classification of azithromycin response was concordant between HS and OS in 210/239 (88%) patients (Fig. 2).

Seven of 29 patients exhibiting disconcordance between HS an OS, demonstrated transient responses in HS. Of the remaining 22 patients, 5 were progressive and 17 were non-progressive.

Sensitivity and specifity of HS in detecting progressive patients resulted in p values of 0.800 and 0.962 respectively. Positive predictive value (PPV) and negative predictive value (NPV) were $p = 0.863$ and $p = 0.941$. Sensitivity and specifity of HS in detecting responder resulted in p values of 0.833 and 0.944 respectively. Positive predictive value (PPV) and negative predictive value (NPV) were $p = 0.761$ and $p = 0.964$. Analysis of concordance between home and clinic spirometry resulted in K

Table 1 Baseline characteristics of patients.

		All patients
N		239
Age	Years	52 (39—59)
Female gender	*N* (%)	121 (51)
Underlying disease		
Emphysema		96 (40)
Pulmonary Fibrosis		48 (20)
Cystic fibrosis		50 (21)
Eisenmenger		28 (12)
Other		17 (7)
Transplant procedure	*N* (%)	
Double lung		184 (77)
Single lung		41 (17)
Heart lung		14 (6)
Calcineur-ininhibitor	*N* (%)	
Cyclosporine		126 (53)
Tacrolimus		113 (47)
Time between transplantation and inclusion	Months	39 (18—68)
BOS stage at start of azithromycin	*N* (%)	
0p		37 (15)
1		97 (41)
2		62 (26)
3		43 (18)
FEV_1 at start of azithromycin	% Baseline	67 (54—77)
Baseline FEV_1	% Predicted	85 (68—100)
Restrictive pattern	*N* (%)	49 (21)
BOS onset post-transplant	Months	34 (16—58)
Airway colonization[a]	*N* (%)	71 (30)
Follow-up after start of azithromycin	Months	22 (11—37)
Rapid decliner before azithromycin (FEV_1 decline $\geq$ 100 ml/month)	*N* (%)	108 (45)
Death during follow-up	*N* (%)	70 (29)
Causes of death	*N* (%)	
- Respiratory failure		41 (59)
- Malignancy		5 (7)
- Cardiovascular disease		5 (7)
- Other		19 (27)
Re-transplantation during follow-up	*N* (%)	13 (5)

Median (Interquartile Range).
[a] Airway colonization with gram-negative bacteria (e.g. Pseudomonas aeruginosa).

values of 0.782 for progressive patients. *K* values for stable patients and responder indicated substantial agreement ($\kappa = 0.782$, $\kappa = 0.749$).

Seventy patients (29%) died during follow-up after 490 (258—1013) days, 59 (84%) in the HS-progressive group. Causes of death are shown in Table 1. Five of 239 (2%) patients died from cardiovascular events (stroke $n = 1$, ST-elevation myocardial infarction $n = 1$, sudden cardiac death $n = 3$). All patients dying following cardiac arrest had advanced chronic allograft dysfunction and were oxygen dependent. Thirteen patients (5%) underwent re-transplantation, all of whom had been HS-progressive. In HS-progressive patients, 44 (75%) died from respiratory failure after 450 (215—989) days.

Median survival of all patients was 1952 (1228—3289) days after transplantation, 756 (379—1302) days after BOS onset and 673 (341—-1106) days after commencing azithromycin. Kaplan—Meier survival estimates at 1 and 3 years after initiation of azithromycin was 91% and 74% for responders versus 69% and 41% for non-responders ($p = 0.005$). Overall survival of progressive and non-progressive patients is displayed Fig. 3.

Worst survival occurred in the HS-progressive group with median survival of 1.0 (0.0—2.0) years. Transient azithromycin responders in HS demonstrated improved survival when compared to azithromycin -refractory patients (2.0; IQR1.0—4.0) years, $p = 0.034$).

BOS onset of BOS was earlier in the progressive group, arising 31 (15—48) months post-transplant compared to 46 (22—73) months amongst non-progressive patients ($p < 0.05$). FEV_1 at azithromycin initiation was also lower 65% Best FEV_1 (IQR 51—75) vs. 70% (69—79) in the non-

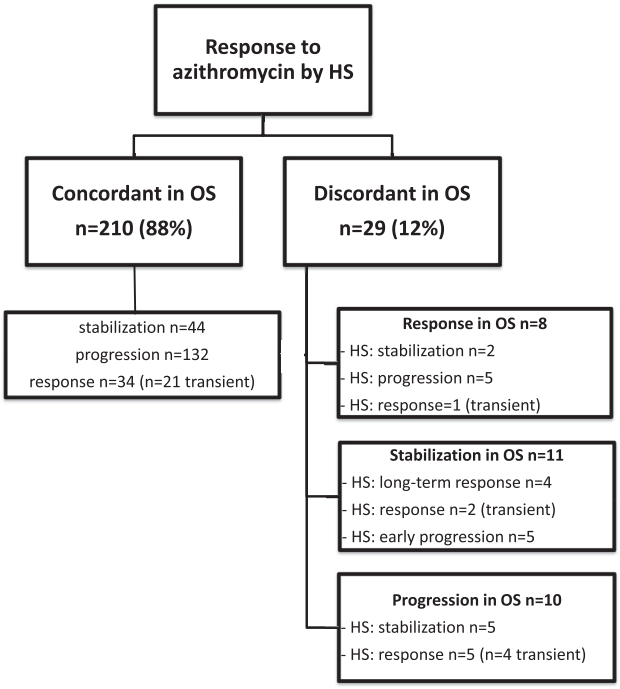

Figure 2 Comparison of home spirometry (HS) and office spirometry (OS) measurements.

progressive group ($p < 0.05$). No significant differences were observed in co-medication (steroid pulse or taper, anti-reflux or pro-kinetic treatments), use of azithromycin loading dose or gram-negative airway colonization between the response groups (Table 2).

Discussion

We describe the utility of home spirometry (HS) in the early detection of macrolide-refractory BOS. HS identified progressive patients more than 4 weeks earlier than office spirometry, whilst achieving acceptable concordance with office spirometry in assessment of macrolide treatment response. Home spirometry has previously been validated in lung transplant populations, with various studies describing benefits in detecting early changes in graft function [11—16]. In a study involving 45 LTx recipients, Finkelstein et al. diagnosed BOS 1 on average 341 days earlier than OS, with those progressing to BOS 2 and 3 being identified 144 days earlier [15]. Our findings confirm high levels of concordance between home spirometry (HS) and office spirometry (OS).

Despite these findings, we continue to support controlling OS 4 weeks after azithromycin initiation due to inadequate HS adherence in some patients. Difficulties in performing the forced expiratory maneuver were suspected in 60% of patients showing greater variability in HS measurements. Although patients were trained in using the home spirometer, the measurements were performed unsupervised, in contrast to OS which was supervised by experienced personnel, allowing direct correction of false technique.

In two thirds of observed discrepancies, trends in pulmonary function were not detected in HS. Additional training on how to perform HS when recipients are being prepared for hospital discharge may improve patient adherence and further improve concordance between HS and OS. We have previously observed greatest adherence

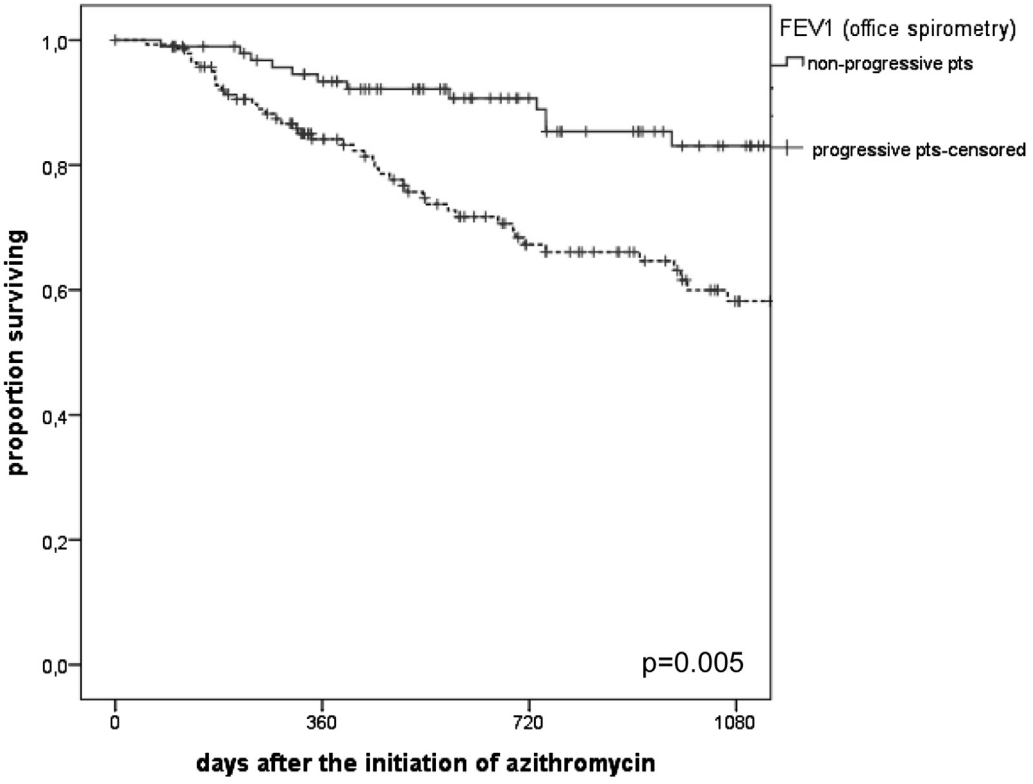

Figure 3 Survival after azithromycin initiation in BOS (office spirometry data).

Table 2 Characteristics of progressive and non-progressive patients based on home spirometry data.

		Progressive patients	Non-progressive patients	*p*-Value
	N (%)	161 (67)	78 (33)	
Age	Years	51 (38—58)	53 (43—61)	0.039
Gender female	*N* (%)	81 (50)	40 (51)	0.888
Cystic fibrosis	*N* (%)	37 (23)	13 (17)	0.261
Gram-negative airway colonization	*N* (%)	48 (30)	23 (30)	0.959
Time between transplantation and initiation	Months	35 (18—64)	43 (19—75)	0.253
Time since onset of BOS	Months	31 (15—48)	46 (22—73)	**0.008**
BOS stage at inclusion	*N* (%)			
0p or 1		84 (52)	50 (64)	0.082
2 or 3		77 (48)	28 (36)	
Baseline FEV_1	% Best	65 (51—75)	70 (60—79)	**0.032**
Use of proton pump inhibitor or H2 receptor blocker	*N* (%)	141 (88)	66 (85)	0.529
Azithromycin loading dose	*N* (%)	55 (34)	26 (33)	0.899
Follow-up after start of azithromycin	Months	22 (10—37)	23 (12—36)	0.606
Re-transplantation during follow-up	*N* (%)	13 (8)	0 (0)	**0.010**
Death during follow-up	*N* (%)	59 (37)	11 (14)	**<0.001**

Median (interquartile range).
Bold values represent that values are statistically significant.

rates with HS in the initial year following transplantation, with a subsequent decrease over time [20]. Annual training updates, reiterating the importance and technique of HS may improve adherence in long-term transplant recipients.

Less than 5% of patients were identified as transient responders or stable in HS, while OS demonstrated progression. It is unsurprising that OS proved less sensitive in identifying transient responders. Temporary improvements in pulmonary function occurring between visits could be potentially missed, in contrast to daily measurements in HS. In half of transient responders, increases in HS FEV_1 appeared implausible, suggesting alternative explanations including that another person may have performed HS on the device.

According to various reports, approximately 35% of patients in different BOS stages respond to macrolide treatment [6,7,21—25]. There exists however no uniform definition of response, and most studies made no distinction between long-term and transient response. Our response rates appear lower and a greater proportion treatment initiation in advanced BOS stages (2 or 3) compared to the largest study [8].

Azithromycin was prescribed at 250 mg orally three times per week, in concordance with the majority of published studies [6,8,21,22], including our own experiences [25]. Very high tissue concentrations, high lipid solubility in combination with a long half-time allow such treatment protocols. To optimize patient adherence we recommended fixed-dosing (Monday—Wednesday—Friday) rather than alternate days. Current experience in CF-populations has demonstrated, that if 250 mg is not effective, higher doses are also generally ineffective and resulted in increased side-effects [20]. Commonest side-effects included nausea, vomiting, diarrhea or abdominal pain. Gastrointestinal intolerance was greatest in daily treatment protocols [30]. In our experience, prolonged use of azithromycin is well tolerated, with at most mild side-effects. No ventricular arrhythmias were observed in our cohort. This may be explained by LTx recipients being typically younger, with proven absence of cardiac disease in contrast to elderly patients with cardiovascular risk factors [31]. Nevertheless 5/239 (2%) patients died from cardiovascular events (stroke $n = 1$, ST-elevation myocardial infarction $n = 1$, sudden cardiac death $n = 3$). Currently we recommend QTc monitoring prior to initiation and regularly during long-term azithromycin along with avoidance of other QTc prolonging drugs.

In accordance with previous studies, macrolide responders demonstrate significantly better overall survival compared to non-responders [8,9]. Interestingly, survival in patients exhibiting a sustained response was similar to those demonstrating a transient response and non-response with stable FEV_1. This may reflect a more benign disease course. Our findings emphasize that even short-term response and stabilization confer patient benefit. Improved functional reserve afforded by short-term response and lung function stabilization may facilitate a more favorable BOS course. In macrolide-refractory patients alternative treatments such as extracorporeal photopheresis [26], total lymphoid irradiation [27], montelukast [28], anti-reflux treatment or re-transplantation remain possible treatment options. Regarding additional clinical risk factors such as gram-negative airway colonization or co-medication, no significant differences between progressive and non-progressive patients were observed.

Additional factors may limit the conclusions beyond the retrospective single-center nature of the study. Bias may exist in patient adherence due to selection criteria (patients without HS and non-adherent patients were not evaluated). Addition of further BOS treatment options following macrolide initiation such as extracorporeal

photopheresis [26], total lymphoid irradiation [27] or montelukast [28] were not considered.

In conclusion, HS appears to be a safe and reliable tool in facilitating assessment of treatment response in patients with BOS commenced on azithromycin. HS detects macrolide-refractory BOS significantly earlier and might help optimize treatment escalation through other available treatments or consideration for re-transplantation. Patients may be instructed to contact their transplant center when a significant decline in FEV_1 is evident on their HS device. Changes in HS should then be confirmed by OS. When long-term use of macrolides is indicated, we recommend outpatient reassessment of treatment response 4 weeks after treatment initiation. Patients with progressive lung function decline detected by OS or HS despite azithromycin therapy should be considered for early escalation of BOS therapy. It remains conceivable, that azithromycin also confers a more favorable BOS clinical course in these patients. Given that BOS is life-threatening, with no superior alternative treatment, we routinely continue long-term azithromycin in patients who stabilize and even in progressive patients if well tolerated. In general, patients decline treatment cessation due to anxiety of further acceleration in FEV_1 decline.

Authorship

Acquisition of data: de Wall, Fuehner, Greer.

Analysis and interpretation of data: de Wall, Dettmer, Welte, Haverich.

Statistical analysis: de Wall, Gottlieb.

Drafting of the manuscript: de Wall, Gottlieb.

Critical revision of the manuscript: Gottlieb, Welte, Warnecke, Haverich, Greer.

Funding sources/disclosure

This work was supported by a grant from the German Federal Ministry of Education and Research (reference number: 01EO0802), the contents of this article are the sole responsibility of the authors. The authors of this manuscript have no conflicts of interest to disclose as described by *Respiratory Medicine*.

Acknowledgments

This work was supported by a grant from the German Federal Ministry of Education and Research (reference number: 01EO0802), the contents of this article are the sole responsibility of the authors.

References

[1] Yusen RD, Christie JD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Dobbels F, Kirk R, Lund LH, Rahmel AO, Stehlik J. The Registry of the International Society for Heart and Lung Transplantation: thirtieth adult lung and heart-lung transplant report — 2013; focus theme: age. J Heart Lung Transpl 2013;32(10):965—78.

[2] Jackson CH, Sharples LD, McNeil K. Acute and chronic onset of bronchiolitis obliterans syndrome (BOS): are they different enteties? J Heart Lung Transpl 2002;21:658—66.

[3] Knoop C, Estenne M. Acute and chronic rejection after lung transplantation. Semin Respir Crit Care Med 2006;27:521—33.

[4] Lama VN, Murray S, Martinez FJ. Course of FEV1 after onset of bronchiolitis obliterans syndrome in lung transplant recipients. Am J Respir Crit Med 2007;175:1192—8.

[5] Cooper JD, Billingham M, Yousen S. A working formulation for the standardization of nomenclature and for clinical staging of chronic dysfunction in lung allografts. International Society of Heart and Lung Transplantation. J Heart Lung Transpl 1993;12:713—6.

[6] Gerhardt SG, McDyer JF, Orens JB. Maintenance azithromycin therapy for bronchiolitis obliterans syndrome: results of a pilot study. Am J Respir Crit Care Med 2003;168:121—5.

[7] Verleden GM, Vanaudenaerde BM, Dupont LJ. Azithromycin reduces airway neutrophilia and Interleukin-8 in patients with bronchiolitis obliterans syndrome. Am J Respir Crit Care Med 2006;174:566—70.

[8] Vos R, Vanaudenaerde BM, Ottevaere A. Long-term azithromycin for bronchiolitis obliterans syndrome: divide and conquer? J Heart Lung Transpl 2010;29:1358.

[9] Jain R, Hachem RR, Walter MJ. Azithromycin is associated with increased survival in lung transplant recipients with bronchiolitis obliterans syndrome. J Heart Lung Transpl 2010;29:531—7.

[10] Vanaudenaerde BM, Vos R, Meyts I. A dichotomy in bronchiolitis obliterans syndrome after lung transplantation revealed by azithromycin therapy. Eur Respir J 2008;32:832.

[11] Bjortuft O, Johansen B, Boe J. Daily home spirometry facilitates early detection of rejection in single lung transplant recipients with emphysema. Eur Respir J 1993;6:705—8.

[12] Lindgren BR, Finkelstein SM, Prasad B. Determination of reliability and validity in home monitoring data of pulmonary function tests following lung transplantation. Res Nurs Health 1997;20:539—50.

[13] Finkelstein SM, Lindgren BR, Prasad B. Reliability and validity of spirometry measurements in a paperless home monitoring program for lung transplantation. Heart Lung 1993;22:523—33.

[14] Finkelstein SM, Snyder M, Edin Stibbe C. Monitoring progress after lung transplantation from home: patient adherence. J Med Eng Technol 1996;20:203—10.

[15] Finkelstein SM, Snyder M, Hertz MI. Staging of bronchiolitis obliterans syndrome using Home spirometry. Chest 2009;116:120—6.

[16] Karl BC, Finkelstein SM, Robiner WN. The design of an internet-based system to maintain home monitoring adherence by lung transplant recipients. IEEE Trans Inform Technol Biomed 2006;10:66.

[17] Estenne M, Maurer RJ, Boehler A. Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. J Heart Lung Transpl 2002;21:297.

[18] Sato M, Waddell T, Keshavjee S. Restrictive allograft syndrome (RAS): a novel form of chronic organ dysfunction. J Heart Lung Transpl 2011;30:735—42.

[19] Miller MR, Hankinson J, Brusasco V. Standardization of spirometry. Eur Respir J 2005;26:319.

[20] Kugler C, Fuehner T, Gottlieb J. Effect of adherence to Home spirometry on bronchiolitis obliterans syndrome and graft survival after lung transplantation. Transplantation 2009;88:129—34.

[21] Verleden GM, Dupont LJ. Azithromycin therapy for patients with bronchiolitis obliterans syndrome after lung transplantation. Transplantation 2004;77:1465—7.

[22] Yates B, Murphy DM, Corris PA. Azithromycin reverses airflow obstruction in established bronchiolitis syndrome. Am J Respir Crit Care Med 2005;172:772—5.
[23] Shitrit D, Bendayan D, Gidon S. Long-term azithromycin use for treatment of bronchiolitis obliterans syndrome in lung transplant recipients. J Heart Lung Transpl 2005;24:1440.
[24] Porhownik NR, Batobara W, Kepron W. Effect of maintenance azithromycin on established bronchiolitis obliterans syndrome in lung transplant patients. Can Respir J 2008;15:199.
[25] Gottlieb J, Szangolies J, Welte T. Long-term azithromycin for bronchiolitis obliterans syndrome after lung transplantation. Transplantation 2008;85:36—41.
[26] Benden C, Speich R, Hofbauer GF. Extracorporeal photopheresis after lung transplantation: a 10-year single-center experience. Transplantation 2008;86:1625—7.
[27] Verleden GM, Lievens Y, Vanaudenaerde BM. Efficiency of total lymphoid irradiation in azithromycin nonresponsive chronic allograft rejection after lung transplantation. Transpl Proc 2009;41:1816—20.
[28] Verleden GM, Verleden SE, Vanaudenaerde BM. Montelukast for bronchiolitis obliterans syndrome after lung transplantation: a pilot study. Transpl Int 2011;24:651—6.
[30] Griffith DE, Brown BA, Girard WM, Griffith BE, Couch LA, Wallace Jr RJ. Azithromycin-containing regimens for treatment of Mycobacterium avium complex lung disease. Clin Infect Dis 2001;32(11):1547—53.
[31] Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. N Engl J Med 2012;366(20):1881—90.